REMARKS

The Office Action dated May 26, 2009 has been reviewed, and the comments of the U.S. Patent Office have been considered. Claims 1,5, 6, 46 and 50 have been amended and Claim 51 has been added. The amendment of claims 1, 5, 6 and 46 does not add new matter. It removes language present in the claims as originally filed but rendered superfluous by subsequent amendments. The amendment to Claim 50 does not add new matter – the specification as originally filed discusses a therapeutic composition comprised of the antibody and a pharmaceutically acceptable excipient, see pages 18 – 19. That these must be acceptable to administration to a variety of mammals is set forth there, as well as page 10 of the specification as originally filed.

New Claim 51 merely combines recitations of previously presented claims.

Entry of the amendments advanced herein is respectfully requested.

Claim Rejections – 35 U.S.C. § 102

Claims 1, 6, 43, 46 and 49-50 remain rejected under 35 U.S.C. 102(b) as being anticipated by Li et al. (IDS, U.S. 5,891,668). This rejection is respectfully traversed.

The Examiner maintains this rejection only by reusing "to give patentable weight" to the limitation that the antibody recited modulates interaction between TSG101 and M2D2. Office Action, page 4. Respectfully, this decision is unsupported by practice and by law. The Examiner is not free to "disregard" those limitations which he cannot find recited in the prior art on the theory that the recitation in question is simply the effect of binding anywhere to a TSG101 protein in its ubiquitination domain. The Examiner may assert its inherent (which the Examiner

later appears to be intent on doing, *infra*, or may indicate that the prior art achieves this result, but the Examiner, Applicants respectfully submit, is not free to simply discard a recitation in the body of the claim.

In fact, Applicants appear to be the first, by the Examiner's own recognition, to discover that certain antibodies that bind to the ubiquitination region do in fact modulate this important interaction, as well as the expression of p53. There is no support, anywhere in the references assembled, and there are LOTS of references assembled, forth proposition that all antibodies of any type that bind to the ubiquitination region of TSG101 modulate the interaction between TSG101 and M2D2. Withdrawal of the rejection on this ground is respectfully traversed.

In point of fact, at pages 5 – 6 f the Office Action, the Examiner appears to give the recitation patentable weight, but insists it is inherent in the binding of an antibody to the ubiquitination region of TSG101, and places the burden on Applicants to demonstrate to the contrary. Respectfully, the Examiner has not made out the *prima facie* case required for such burden shifting.

The reference, Li et al, does not **exemplify any** antibodies. It does in fact have a suggestion that antibodies might be usefully made to regions of TSG101 other than the ubiquitination domain, specifically in diagnostics. It does not identify an antibody, it does not provide the method by which such an antibody should be made, the sequence for such a putative antibody, or anything else to guide a practitioner to a given antibody. It is, in fact, a pioneering description of the character and properties of a newly discovered host protein associated with a variety of essential biological processes – it does not focus on the antibodies, nor does it describe any biological properties of these antibodies.

As noted by the Examiner – when the examiner comes forward with a *prima facie* case of prior art inherent anticipation – that is, when the Examiner advances a discrete teaching of the art that indicates that a particular embodiment has a character which should render the recited properties of the claims inherent, then the Applicant must compare his claimed subject matter with that identified by the Examiner. That is not possible herein, because the Examiner has not presented an embodiment or teaching with which to compare the claimed invention. What antibody shall applicants compare their invention to? There is no antibody taught by the reference. While there is a generic reference to the well known Laboratory Manual from Cold Spring Harbor, sufficient to get one of skill in the art to antibodies suitable for in vitro "diagnostic assays for carcinomas and other tumors" and, more specifically, for "staging, detection and typing", Column 9, lines 22 – 30, there is no specific method taught. Respectfully, the burden is on the Patent Office, *imprimus*, to identify specifically WHAT it is that is believed to inherently possess the attributes Applicants claims recite – so that a comparison can be made. *In re Best*, 195 USPQ 430, 432 (CCPA 1977).

Respectfully, Applicants submit that, unlike the situation in *Best*, where the prior art, Hanson, disclosed a specific process cool down method, here the art is so speculative as to specific antibodies that no comparison can be made. Nonetheless, if the Examiner can identify a specific antibody based on the reference for comparison, Applicants will endeavor to provide the type of comparison provided. In the absence of such identification, the rejection must be withdrawn. In this respect, it is noted that simply saying – an antibody to the leucine rich domain, is not enough. An antibody raised by what method, suing what immunogen, etc. Otherwise, the properties will vary.

As the rejection relies on a teaching that, as to properties of the antibodies, simply lacks the teaching to be able to formulate an opinion as to whether all antibodies that bind to the ubiquitination region of TSG101 modulate interaction between TSG101 and M2D2, the rejection is respectfully traversed. There is nothing in the art cited sufficient to support the Examiner's conclusion that this is a property inherent in all antibodies that bind to the proline rich domain of TSG101 modulates the interaction between TSG101 and M2D2.

The Rejection of Claims 43 and 50 is Inapt

In the claims rejected for anticipation over Li et al, the Examiner includes Claims 43 and 50 (and presumably, newly presented Claim 51). These claims require more than an antibody – they require it in a pharmaceutically acceptable excipient – i.e., one that can be safely administered to a mammal *in vivo*. The Examiner concedes that "Li et al does not disclose a pharmaceutical composition as claimed." Office Action, page 5. In particular, as noted by the Examiner, Li discloses the utility of antibodies as useful in vitro diagnostic procedures, such as staining. Office Action, page 5, reference, Column 9. As such, the Examiner argues:

> It would necessarily flow from the teachings of the prior art that the antibody is in a composition comprising an excipients such as a buffer." Office Action, page 6.

Respectfully, the chemistry and the law relied on by the Examiner is incorrect. First the chemistry. Excipients provide a variety of functions, but most importantly, they assist in making the active agent available to the body. Applicants have set forth, immediately below, the outline of the article from Wikipedia ™, an online dictionary, the various types of excipients:

- 1 Types of excipients
  - 1.1 Antiadherents
  - 1.2 Binders
  - 1.3 Coatings

        - 1.3.1 Changing the dissolution rates of active species
    - 1.4 Disintegrants
    - 1.5 Fillers and diluents
    - 1.6 Flavours
    - 1.7 Colours
    - 1.8 Glidants
    - 1.9 Lubricants
    - 1.10 Preservatives
    - 1.11 Sorbents
    - 1.12 Sweeteners

None of these are buffers. Tauber's Medical Dictionary is more direct – it describes excipients as "substances added to a medicine so that it can be formed in to the proper shape and consistency; the vehicle for the drug." In contrast, buffers are ionically active, according to Tauber's, they "react with strong acids or bases to prevent large changes in the pH of the body fluids." The two are totally different. In contrat to excipients, buffers can be and frequently are hazardous to mammals. Tween 20® is a well known buffering agent for staining preparations – apparently the kind of buffer the examiner suggest "flows naturally" for the reference. This is the warning provided by the manufacturers of Tween 20:

> Precautions:
> This product is not classified as hazardous. The preservative used in this reagent is Proclin 300 and the concentration is less than 0.25%. Overexposure to Proclin 300 can cause skin and eye irritation and irritation to mucous membranes and upper respiratory tract. The concentration of Proclin 300 in this product does not meet the OSHA criteria for a hazardous substance. Wear disposable gloves when handling reagents.

Is the Examiner seriously suggesting that this is the type of compound one prepares a pharmaceutical with?

Further, Applicants respectfully submit the law does not embrace, within 35 USC §102 that "which flows naturally from a reference." Either the reference expressly or inherently teaches each and every recitation of the reference, or it does not anticipate. Li et al does not imagine that the antibodies recited would be prepared in a pharmaceutically acceptable excipient. It does not anticipate.

For all of the foregoing, the rejection is respectfully traversed.

Claims Rejections – 35 U.S.C. § 112

Claims 1, 4-6, 43 and 46-50 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. This rejection is respectfully submitted to be mooted by amendment. The Examiner's rejection apparently focuses on the "functional fragment" limitation of the claims. While Applicants respectfully submit that the application as filed clearly demonstrates Applicant's possession and teaching of this concept – see the definition at page 12 of the specification as filed. Resolution of this issue is unnecessary however – the recitation became moot due to subsequent amendments, and so has been deleted. Withdrawal is respectfully requested.

Claims 43 and 50 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. This rejection is respectfully traversed.

The Examiner's rejection appears to be rpremised on a limitation that does not appear within the claims – that these compositions are used to alleviate cancer, in particular, solid tumors. The Examiner sites to no less than 6 references directed to the treatment of solid tumors

with antibodies, to establish the principle that treating cancer with antibodies is difficult, and that Applicants fail to provide sufficient teaching to overcome this understanding of the art. Granted.

The problem with the rejection is that Applicant's claims are in no wise directed to, recite, or involve the cure for cancer. Turning first to Claim 43 (which serves to exemplify Claim 50 as well) – this claim recites two separate elements, an antibody, and an excipient:

> A pharmaceutical composition for treatment of diseases involving TSG 101-mediated ubiquitination, comprising:
> an isolated monoclonal antibody that binds specifically to a polypeptide comprising an ubiquitination-regulating domain, ~~or a functional fragment thereof,~~ of a human TSG101 protein comprising the amino acid sequence of SEQ ID NO:1, wherein said antibody binds specifically to said ubiquitination-regulating domain, ~~or functional fragment thereof,~~ wherein said antibody binds specifically to an epitope in the ubiquitination regulating domain of TSG101 protein found in amino acid residues 1-250 of SEQ ID NO: 1, and a pharmaceutically acceptable excipient.

As observed by the Examiner, the recitation in the preamble is not accorded patentable significance, nor was it intended to. Clearly, there are applications, such as controlling the expression of M2D2, which the antibodies are susceptible of being sued for, which do not require the treatment of solid tumors. As noted in the specification as originally filed, modulating the level of M2D2 in a mammal can have an impact on a wide variety of conditions – see pages 4 – 10. While Applicants agree that it would be great if these antibodies were a treatment or cure for cancer – they are not being claimed as such in this application.

The rejection is respectfully traversed.

Claim Rejections – 35 U.S.C. § 103

Claims 4-5 and 47-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Li et al. (IDS, U.S. 5,891,668, 1999) as applied to claims 1, 6, 43, 46 and 49-50 above, and further in view of Ferrer et al. (Oncogene 1999; 18:2253-2259, IDS).

This rejection is premised on the observation that the various regions of the TSG101 protein bound by the antibodies recited in these claims are known, and therefore, it would be *prima facie* obvious to make antibodies that bind to these regions. The rejection is respectfully traversed.

The Examiner cites for precedent to support his position that knowing the entire sequence of a protein, it is obvious to prepare antibodies to any portion of that sequence, *Ex parte Sugimoto*, 14 USPQ2d 1312 (BPAI 1990). Respectfully, no part of this decision so much as refers to antibodies. It looks to the expectations of a cell which is known to produce various immune response suppressors. The rejection, to the extent it relies on this decision, is respectfully traversed.

The other precedent the Examiner relies on for the sweeping proposition that given a protein, making an antibody to any specific region or domain is obvious, is *Ex parte Ehrlich*, 2 USPQ2d 1011 (BPAI 1987). While this case is closer, it is still wide of the mark. It does find certain antibodies to be obvious – it does NOT find all antibodies to known proteins to be obvious. To arrive at the affirmance in *Ehrlich*, the Board relied on three critical pieces of prior art. 1) Stewart et al – which established that human fibroblast interferon is antigenic. 2) Kohler and Milstein, which set forth a basic method for making hybridoma which express antibodies. 3) Secher which taught that the techniques of Kohler & Milstein may be successfully applied to human interferon. 3 USPQ2d at 1014 – 1015. Respectfully, the Examiner here lacks references to establish items 1, 2 or 3, as applied to TSG101.

With respect to item 1, the establishment that TSG101 is antigenic, the Examiner advances no reference that establishes this. Li et al has been discussed above. While it describes a variety of ways to use antibodies, it does not demonstrate anywhere the TSG101 is itself

antigenic, as opposed to fragments of that protein. One of skill in the art would not immediately jump to that conclusion. In contrast to interferon, which is a chemical designed to initiate antibody challenge in response to invaders and foreign presence in the blood, TSG101 is one of a family of proteins known as ESCRT proteins that move proteins and other chemicals within the cell from one point in the cell to another. What is it the Examiner relies on to conclude these innocent and common host proteins are antigenic?

With respect to item 2, there is no teaching in Li et al that the methods of Kohler & Milstein, or any other protocol for making antibodies, can be successfully used to form the specific antibodies of the claims presented herein, or any other specific kind of antibody, from TSG101. Again, TSG101 is a common mammalian protein. Asserting that it is antigenic, and subject to the Kohler & Milstein technology, is like saying red blood cells are antigenic. It might well be, but it is not self-evident. Needless to say, Ferrer, which does not even address antibodies, does not add to the necessary teaching.

As to item 3, where is the teaching required for the outcome in Ehrlich, that in fact the Kohler & Milstein practices can be successfully applied to the class of compounds in which TSG101 is found. As observed above, TSG101 is an ESCRT protein – it is frequently involved in the migration, intracellularly, from one point to another. For the holding in Ehrlich to be applicable, there would need to be a fundamental teaching that this class of proteins lends itself to the K&M technology. There simply is none.

Respectfully, the Examiner has overstated the law. There is no broad precedent for the proposition that once a protein is identified, the preparation of an antibody to any given epitope, even those not identified as preferential, is obvious. The case law relied on is either not applicable at all, *Sugimoto*, or is far more limited than the Examiner's proposition of law,

Ehrlich. At a minimum, it would require a reference or group of references like those in *Ehrlich,* that is, references that establish that TSG101 is antigenic, that Kohler Milstein technology is useful to prepare antibodies, and that the Kohler Milstein technology has been successfully applied to other proteins of this type to generate antibodies.

At a minimum, even then – it would require a teaching to select the ubiquitination domain for binding, to teach the rejected claims. This is nowhere found in the art. Acordingly, the rejection is respectfully traversed.

CONCLUSION

In view of the foregoing evidence and remarks, Applicants respectfully request reconsideration of this Application and the prompt allowance of at least Claims 1, 4-6, 43 and 46-51.

Should the Examiner feel that there are any issues outstanding after consideration of this response, the Examiner is invited to contact the undersigned to expedite prosecution of the application.

The Commissioner is hereby authorized by this paper to charge any fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0548.

Date: August 26, 2009

Respectfully submitted,

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